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The Beckmann Rearrangement Involving Optically Active Radicals

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The Beckmann Rearrangement Involving Optically Active Radicals

A DISSERTATION

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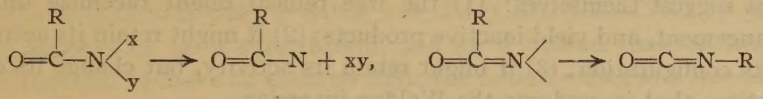
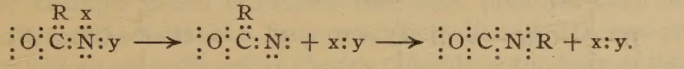
THE BECKMANN REARRANGEMENT INVOLVING OPTICALLY ACTIVE RADICALS

Introduction

Extensive investigations of certain halogen amides, acid azides and hydroxamic acids which undergo rearrangement led Stieglitz[1] to propose that the rearrangements take place in the following manner.



In terms of modern valence relationships, Jones and Hurd[2] have suggested an interpretation of the mechanism of these rearrangements based upon the modern conception of chemical bonds and electrons. Their general formulation excluded the oximes. Thus:



From this interpretation it was assumed that the radical R in its wandering from the carbon atom to the nitrogen atom existed momentarily as a free radical, and that the relative ease of rearrangement of such types of compounds might depend upon the tendency of the radical R in the univalent nitrogen derivative to exist as a free radical.

This hypothesis has been tested by Jones and Hurd,[2] who studied the rearrangement of monophenyl-, diphenyl- and triphenyl-acethydroxamic acids and their derivatives. They found that the relative ease of rearrangement was greater with triphenyl-acethydroxamic acid derivatives than with similar compounds in the diphenyl, or monophenyl series, a fact wholly in agreement with their hypothesis.

Further evidence in support of this hypothesis was submitted by Hurd.[3] Derivatives of N-diphenyl-hydroxyurea, $(C_6H_5)_2N.CO.NHOH$, in which the radical R is potentially a free radical, were found to rearrange; but

[1] Stieglitz, *Am. Chem. J.*, **18**, 751 (1896); *ibid.*, **29**, 49 (1903). Stieglitz and Earle, *ibid.*, **30**, 399, 412 (1903). Stieglitz and Slossen, *Ber.*, **28**, 3265 (1895); *Ber.*, **34**, 1613 (1901). Stieglitz and Leech, *J. Am. Chem. Soc.*, **36**, 272 (1914).

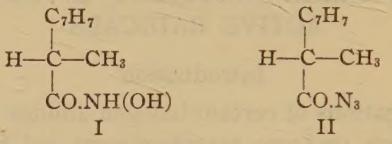
[2] Jones and Hurd, *J. Am. Chem. Soc.*, **43**, 2422 (1921).

[3] Hurd, *ibid.*, **45**, 1472 (1923).

this rearrangement did not occur in the corresponding derivatives of N-monophenyl-hydroxyurea.

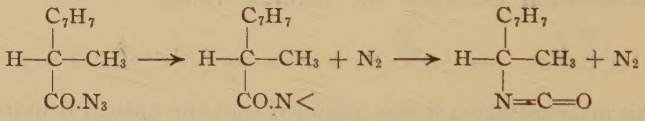
Rearrangement of Derivatives of *d*-Benzylmethylacetic Acid

We have continued these investigations in order to determine the nature of the products formed by rearrangement when the group R is an optically active radical. For this purpose, *d*-benzylmethyl-acethydroxamic acid (I), including some of its derivatives, and *d*-benzylmethyl-acetazide (II) have been prepared and studied.



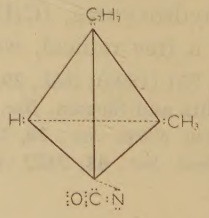
From the viewpoint of the hypothesis stated above three possible mechanisms suggest themselves: (1) the free radical might racemize during rearrangement, and yield inactive products; (2) it might retain its activity and its configuration; (3) it might retain its activity, but change its configuration, that is, undergo the Walden inversion.

The first assumption was excluded by our experiments with *d*-benzylmethyl-acetazide, which rearranged with great readiness to give an *optically active isocyanate.*



This isocyanate, when hydrolyzed, gave an optically active amine hydrochloride and with ammonia an optically active monosubstituted urea.

These results suggest two possible interpretations. It might be assumed that the rearranging group R does not exist as a free radical but that, in some way, before the group actually parts company with its carbon neighbor, the univalent nitrogen atom has begun already to exercise its influence on the radical, in such a manner that when cleavage actually does take place, a change in the configuration of the groups about the asymmetric carbon atom is prevented. This influence might be imagined to be of the nature of a partial valence. A picture of the univalent nitrogen derivative on this assumption is given below:



On the other hand, a survey of the properties of other optically active compounds previously described in the literature implies that this assumption is unnecessary. There are many reactions in which substitution of one group for another directly attached to an asymmetric carbon atom does not lead to racemization. These reactions fall into two classes: (1) those in which the original configuration of the molecule containing the asymmetric carbon atom is maintained; (2) those in which the Walden inversion occurs. Such a classification, however, is not a sharp one, since the reagents employed determine what the course of the reaction will be. Thus, McKenzie and Clough[4] have shown that replacement of the hydroxyl group of some optically active carbinols by chlorine, when phosphorus pentachloride is used as a reagent, produces racemization and inversion, but when thionyl chloride is employed, neither racemization nor inversion is appreciable. Thus, *d*-phenylmethyl-carbinol with thionyl chloride gave *d*-phenylmethylmethyl chloride.

$$2\ d\text{-}(C_6H_5)(CH_3)CH(OH) + SOCl_2 \longrightarrow 2\ d\text{-}(C_6H_5)(CH_3)CHCl + H_2SO_3.$$

This appears to be a substitution, and for a limited time, at least the time required to make an electron shift, the radical exists as a free radical. If we suppose, as is probably the case, that the hydroxyl group as it leaves the sphere of influence of the asymmetric carbon atom takes its electrons with it, and so becomes an hydroxide ion, then the radical would be a positive radical of the nature of a carbonium ion.

Another example which illustrates this same principle may be cited. An optically active sulfonium bromocamphorsulfonate III was prepared by Smiles[5] and an optically active thetine chloride in the form of its chloroplatinate IV, by Pope and Peachey.[6]

Thus $\left[\begin{matrix}CH_3\\ |\\ C_2H_5SCH_2COC_6H_5\end{matrix}\right]^+ C_{10}H_{14}BrOSO_3^-$ III

$\left[\begin{matrix}CH_3\\ |\\ C_2H_5SCH_2COOH\end{matrix}\right]_2^+ PtCl_6^{--}$ IV

Both of these salts possess a rotation which is attributed to the presence of an asymmetric sulfur atom. Although they exist in aqueous solution in the form of their respective ions, racemization is not appreciable. It is evident, therefore, that a positive ion of the above type behaves as if it maintained a configuration approaching that of an asymmetric molecule, even though only three groups are linked directly to the sulfur atom. In this respect these radicals appear to resemble the radical of phenylmethyl-carbinol in the illustration discussed above.

These illustrations make it probable that, in the rearrangement of *d*-benzylmethyl-acetazide, the optically active radical R may exist momentarily as a free radical and maintain a configuration required to produce

[4] McKenzie and Clough, *Trans. Chem. Soc.*, **97**, 2564 (1910).

[5] Smiles, *Trans Chem. Soc.*, **77**, 1174 (1900).

[6] Pope and Peachey, *ibid.*, **77**, 1072 (1900).

an optically active rearrangement product. For, if we suppose, as has been assumed for a long time, that the radical R is a positive radical,[7] and that, in its wandering from the carbon atom to the nitrogen atom, it does not take with it the pair of electrons which it shared with the carbon atom, the analogy of this case to the illustrations given above will be apparent.

The third alternative suggested (p. 170) as a possible mechanism can be eliminated by the following consideration; all the substances prepared directly or indirectly from *d*-benzylmethyl-acetazide were dextro-rotatory. No reagent of the kind employed to bring about inversion was used; the azide, dissolved in benzene, rearranged at 35°.

The Rearrangement of *d*-Benzylmethyl-acethydroxamic Acid and its Derivatives, $(C_7H_7)(CH_3)CH.CO.NHOH$.—This acid, prepared by the action of hydroxylamine upon methyl *d*-benzylmethylacetate in the presence of sodium ethylate, is a colorless solid melting at 121.5°. Its specific rotation[8] in alcohol at 20° is +63.2°. The benzoyl ester of this acid, $(C_7H_7)(CH_3)CH.CO.NHOCO.C_6H_5$, under similar conditions gave a specific rotation of +54.5°, and was found capable of forming salts. The solid potassium salt, in one experiment, decomposed spontaneously at room temperature. When this salt was dissolved in cold water, the clear solution first formed became milky at 15–20°, and the odor of isocyanate was very easily detected. Hydrolysis of the isocyanate took place very slowly at room temperature, but when the solution was boiled *sym.*-dibenzylmethylmethyl-urea was produced. This urea melted at 198°, and a dilute solution of it in alcohol showed no appreciable rotation.

$$(C_7H_7)(CH_3)CH.CO.NKOCO.C_6H_5 \longrightarrow (C_7H_7)(CH_3)CH.NCO + C_6H_5COOK$$
$$2(C_7H_7)(CH_3)CH.NCO + H_2O \longrightarrow [(C_7H_7)(CH_3)CH.NH]_2CO + CO_2$$

The racemic (*dl*) and mixed[9] levo forms of this acid, and their derivatives were also prepared. A comparison of their properties will be found in the experimental part.

The Rearrangement of *d*-Benzylmethyl-acetazide, $(C_7H_7)(CH_3)CH.CO.N_3$.—This compound was prepared by the action of sodium azide on *d*-benzylmethyl-acetyl chloride dissolved in ether. It was a colorless liquid so unstable that decomposition occurred slowly even at 10°. If moisture be present decomposition seems to take place at a lower temperature.

Its rotation in a 50mm. tube at 5° without solvent was +30.77°. When it was dissolved in benzene, nitrogen began to be evolved at 15–20°, and at 35° the decomposition was moderately rapid.

[7] Jones, *Am. Chem. J.*, **50**, 441 (1913).

[8] The specific rotation was calculated from the formula $[\alpha]_D^{20} = 100\alpha/l.c$ where c is the number of grams of substance in 100 cc. of solution.

[9] The levo modification was not obtained in a pure form. Fractional crystallization of benzylmethylacetic acid gives only the pure *d*-isomer, and consequently all derivatives which were prepared from the mixed levo acid contain the racemic modification as well.

The relative ease of rearrangement of this acid azide made it possible to carry out experiments on the velocity of its rearrangement. Few attempts have been made to determine the order of reaction in rearrangements of this kind by measurements of their velocities. Dougherty and Jones[10] studied the rearrangement of the potassium salt of dibenzhydroxamic acid, and measured the velocity of its rearrangement. For at least 75% of the reaction time the velocity corresponded to that of a unimolecular reaction. But there were side reactions which complicated the problem, and other experimental difficulties were involved.

No such complications were encountered in this case. The velocity was measured by the amount of nitrogen gas evolved in a given time. The velocity of rearrangement corresponded to that of a unimolecular reaction; the mean value of $k_{35°}$ as calculated from the equation[11] was .01178.

When the *d*-azide rearranged in benzene it gave a liquid isocyanate which boiled at 82° (5 mm.). This isocyanate in a 50mm. tube at 20° without solvent gave a rotation of +28.75°. The decomposition of the azide to the isocyanate, as measured by the amount of nitrogen evolved, is nearly quantitative. In one experiment 97% of the calculated amount of nitrogen was collected. The isocyanate was found to be easily hydrolyzed by concd. hydrochloric acid at a relatively low temperature. The amine, obtained as the hydrochloride and dissolved in water, gave a specific rotation of +16.6°, at 20°.

Ammonia reacted with the *d*-isocyanate to form the monosubstituted urea, a crystalline compound melting at 136°; its specific rotation in acetone at 20° was found to be +10.7°. The racemic monosubstituted urea, prepared in a similar manner, melted at 149°. $(C_7H_7)(CH_3)CH.NCO + NH_3 \longrightarrow (C_7H_7)(CH_3)CH.NHCONH_2$.

The *sym.*-di-benzylmethylmethyl-urea, however, prepared from the *d*-isocyanate gave no appreciable rotation when dissolved in alcohol. Here, as in the case of the hydroxamic acid, a white crystalline solid was obtained melting at 197–198°, a melting point practically identical with that of the urea prepared from *d*- and from *dl*-benzylmethyl-acethydroxamic acids, and from the *dl*-azide. Two possible explanations of this may be offered. The hydrolysis of benzylmethyl-methylisocyanate by water required a temperature of 80–90°. This might have caused racemization of the urea. There is another factor also; this urea is not very soluble at room temperature in organic solvents,[12] and only small concentrations could be used for polarimetric observations. If this urea possessed a low specific rotation, it would not be possible with the concentrations used, to obtain an appreciable reading. The fact that the melting points of the

[10] Dougherty and Jones, *J. Am. Chem. Soc.*, **46**, 1535 (1924).

[11] The equation is $k = 2.303/t_n\ [\log_{10} V_\infty - \log_{10}(V_\infty - V_n)]$.

[12] The approximate solubility of this urea is 0.60 g. in 50 cc. of methyl alcohol.

urea prepared from the *d*, the *l* and the *dl*, forms of the hydroxamic acid, and from the azide, are the same, seems to indicate racemization as the more probable explanation.

Experimental Part

d-Benzylmethyl-acethydroxamic Acid

$(C_7H_7)(CH_3)CH.CO.NHOH$

Preparation of *d*-Benzylmethylacetic Acid.—The preparation of this acid has been described by several investigators.[13] The acid used in the following experiments was prepared from ethyl aceto-acetate according to the method of Conrad with a few modifications. Better yields of the acid were obtained when methylation of the ester preceded benzylation. We found that ethyl benzylaceto-acetate is partially decomposed on distillation, an observation not in agreement with the statement of Conrad, but confirmed by Ehrlich.[14] Ethyl benzylmethylaceto-acetate was saponified without previous distillation; the impurities present do not affect the purity of the acid, since subsequent distillation removes them. Better results were obtained when about 50 g. of potassium hydroxide in excess of the calculated amount dissolved in 50% alcohol was employed to decompose 125 g. of the ester. Much time was saved since the alcohol provides a medium in which the ester is soluble, and less ketone is produced by this method than by the method of Kipping and Hunter.

The acid boiled at 144° (9 mm.). After much difficulty it was converted into a solid that melted at 36.5°. The melting point recorded by Conrad is 37°. The boiling point recorded by Kipping and Hunter is 160° (20 mm.).

The acid was resolved into its optically active isomers by the method of Kipping and Hunter.[13c] Dil. alcohol as the crystallizing medium for the *d*-quinine salts was found to give the best results, and six crystallizations gave a salt melting at 120–121°. Three portions of the acid, liberated from this quinine salt by dil. sulfuric acid, gave the following rotations at 20° without solvent in a 100mm. tube: +20.10°; +20.74°; +20.35°. From 100 g. of the racemic acid 20 g. of *d*-benzylmethylacetic acid was obtained.

The residue from the fractional crystallizations gave 50 g. of a mixed *levo* acid of a rotation of —9.56°, without solvent in a 100mm. tube at 20°.

Preparation of the Methyl Ester of the Dextro Acid, $(C_7H_7)(CH_3)$-$CH.CO.OCH_3$.—This ester is not described in the literature.

Thirty g. of *d*-benzylmethylacetic acid was added to 40 cc. of anhydrous methyl alcohol, and the mixture cooled to 0°. Dry hydrogen chloride was passed through

[13] (a) Conrad and Bischoff, *Ann.*, **204**, 177 (1880). (b) Conrad, *Ber.*, **11**, 1055, 1058 (1878). (c) Kipping and Hunter, *Trans. Chem. Soc.*, **83**, 1005 (1903). (d) Lapworth and Lenton, *Proc. Chem. Soc.*, **18**, 35 (1903).

[14] Ehrlich, *Ann.*, **187**, 13 (1879).

the solution. The temperature was allowed to rise slowly until 30° was reached, and then maintained constant for one hour. The mixture acquired a deep orange color, but when the liquid was cooled and poured into ice water, this color disappeared. The ester was extracted with ether, washed with a solution of sodium carbonate and dried with anhydrous sodium sulfate. When the ether was evaporated in a vacuum, the ester was obtained as a colorless liquid of a pleasant odor; yield, 25 g. It gave a rotation of +26.75° at 20° without solvent in a 100mm. tube. The racemic ester was also prepared, as well as a mixed levo modification. The rotation for the latter under conditions similar to those employed with the dextro form was —12.66°.

Preparation of *d*-Benzylmethyl-acethydroxamic Acid, $(C_7H_7)(CH_3)$-CH.CO.NHOH.—Action of Free Hydroxylamine on the Methyl Ester. Free hydroxylamine was prepared from the hydrochloride according to the method of Lecher and Hofmann.[15]

The ester, dissolved in ethyl alcohol, and treated with free hydroxylamine gave no test for monohydroxamic acid with ferric chloride after three days. Addition of an equivalent of sodium ethylate, however, caused the reaction to take place in a few minutes. The hydroxamic acid so formed was recovered by means of its copper salt as described below.

Four g. of hydroxylamine hydrochloride (recrystallized from alcohol) was dissolved in absolute alcohol, and converted into a solution of the free base by the addition of an equivalent amount of sodium ethylate. The sodium chloride was collected on a filter, and the solution of free hydroxylamine, so formed, added to an alcoholic solution containing 10 g. of the ester. At the same time sodium ethylate, made by dissolving 1.4 g. of sodium in 25 cc. of alcohol, was added. After three minutes a decided test for the hydroxamic acid was obtained with ferric chloride. The solution was evaporated to dryness at room temperature in a current of dry air; crystals of the sodium salt of the hydroxamic acid separated. This salt was dissolved in 100 cc. of water, the solution acidified with acetic acid and a saturated solution of copper acetate added in excess. The precipitated copper salt was collected on a filter, washed with ether, thoroughly dried and ground to a fine powder.

The copper salt was next suspended in 200 cc. of ether, and dry hydrogen sulfide gas passed[16] through the mixture until all of the salt was decomposed, and the copper precipitated as the sulfide.

The ether solution of the free hydroxamic acid was evaporated to dryness, and the solid acid was dissolved in ethyl acetate and precipitated with ligroin. Two crystallizations gave a crystalline compound melting at 121.5°. A solution of 1.2847 g. in ethyl alcohol, diluted to 50 cc., gave a rotation of +3.25° in a 200mm. tube at 20°; $[\alpha]_D^{20°} = +63.2$.

In a similar manner *dl*-benzylmethyl-acethydroxamic acid was prepared; m. p., 124.4°.

The melting point of the mixed levo form was 118.5–120°. A solution of 1.1090 g. in ethyl alcohol diluted to 50 cc. gave a rotation of —1.38° in a 200mm. tube at 20°; $[\alpha]_D^{20°} = -31.1$.

These optically active acids, allowed to stand for 12 weeks, showed no appreciable racemization.

[15] Lecher and Hofmann, *Ber.*, **55**, 912 (1922). An improved method has been recently described by Hurd [*J. Am. Chem. Soc.*, **47**, 67 (1925)]. Better yields of the free base are claimed to be obtained.

[16] Alcohol was tried but this gives a strong odor of mercaptan.

The benzylmethyl-acethydroxamic acids are white crystalline solids, soluble in alcohol, in acetone, in ether, in ethyl acetate and in hot water. They are somewhat soluble in cold water, and very slightly soluble in ligroin and benzene.

Anal. *dl*-Acid. Subs., 0.4164: N, 29.8 cc. (27°, 750 mm.), over water. Calcd.: N, 7.82. Found: 7.74.

d-Acid. Subs., 0.3763: N, 25.4 cc. (22°, 760 mm.), over water. Found: 7.64.

Mixed *l*-acid. Subs., 0.2859: N, 19.9 cc. (20°, 758 mm.), over water. Found: 7.90.

The Benzoyl Ester of *dl*-Benzylmethyl-acethydroxamic Acid, $(C_7H_7)(CH_3)CH.CO.NHOCO.C_6H_5$.—METHOD I. SCHOTTEN-BAUMANN REACTION.

Four g. of *dl*-benzylmethyl-acethydroxamic acid was dissolved in a quantity of warm solution of potassium hydroxide just sufficient to cause solution. Then 2.7 cc. of benzoyl chloride was added in three portions. The reaction mixture was constantly agitated for 15 minutes, and kept cool by allowing water to play over the flask. Thus, 6.1 g. of crude dry product was obtained. Three crystallizations of it from ethyl acetate and ligroin gave a compound melting at 119–119.5°.

METHOD II. MODIFICATION OF SCHOTTEN-BAUMANN REACTION.

Method of Jacobs and Heidelberger.[17]

Two g. of *dl*-benzylmethyl-acethydroxamic acid was dissolved in 10 cc. of glacial acetic acid, and 10 cc. of a saturated solution of sodium acetate added. Benzoyl chloride was added drop by drop until a test with ferric chloride gave no color reaction. The flask was shaken vigorously and kept cool by running water; yield, 3.6 g. of crude, dry product. Two recrystallizations from ethyl acetate and ligroin gave an ester melting at 119–120°.

Of the two methods, Method II requires less time and is more convenient.

The Benzoyl Ester of the *d*-Benzylmethyl-acethydroxamic Acid.—This ester was prepared according to Method II. After two recrystallizations, it melted at 116°.

A solution of 1.0054 g. in alcohol, total volume 50 cc., gave a rotation of +4.40° in a 100mm. tube, at 20°; $[\alpha]_D^{20°} = +54.5°$.

The mixed levo ester prepared in a similar manner melted at 114–116°, and 0.5143 g. dissolved in alcohol, and diluted to 50 cc. gave a rotation of —0.52 in a 100mm. tube at $[\alpha]_D^{20°} = -25.3°$.

These esters are white solids, soluble in acetone, in ethyl acetate, in chloroform, in ether, in hot benzene and in alcohol. They are insoluble in water, and very slightly soluble in cold ligroin and sodium hydroxide solution. When a solution of either ester in a dilute solution of sodium hydroxide was warmed, rearrangement occurred.

Anal. *dl*-Ester. Subs., 0.3138: N, 14.5 cc. (25°, 756 mm.), over water. Calcd.: N, 4.95. Found: 5.10.

d-Ester. Subs., 0.4330: N, 20.2 cc. (25°, 746 mm.), over water. Found: 5.08.

[17] Jacobs and Heidelberger, *J. Am. Chem. Soc.*, **39**, 1441 (1917).

Potassium Salt.—An alcoholic solution of potassium ethylate was prepared of such strength that 1 cc. was equivalent to 0.039 g. of potassium.

One g. of the *dl*-benzoyl ester was suspended in 10 cc. of dry ether, and boiling alcohol was added drop by drop until the ester was completely dissolved. The clear solution was cooled to —12°, and 3.6 cc. of potassium ethylate solution added. No precipitate of the potassium salt occurred until the solution had been diluted largely with dry ether previously cooled to —10°. The salt, precipitated as a white crystalline substance, was allowed to settle for half an hour. It was then collected on a filter quickly, and placed in a vacuum desiccator to dry. When it was taken out into the air it puffed suddenly, spontaneous rearrangement took place, and the sharp odor of isocyanate was very easily detected in the cloud of vapors. The residue on the watch glass, dissolved in water, formed a turbid solution, from which *sym.*-di-benzylmethylmethyl-urea separated when it was boiled. Recrystallized from hot acetone, this urea melted at 198°.

At only one time in these experiments was it possible to obtain a weight of the potassium salt, for rearrangement occurred spontaneously when the dry salt was taken out into the air. In this instance 2.00 g. of the ester gave 2.01 g. of the potassium salt. This shows that in this experiment the salt was precipitated from the ether solution to the extent of 85%.

Several experiments were carried out in which the method of procedure described above was varied. Special attention was given to the effect of a rise in temperature, excess of potassium ethylate, and an increase in the volume of alcohol. When much more alcohol was added than was necessary for the solution of the benzoyl derivative, ether failed to give a complete precipitation of the potassium salt. An excess of potassium ethylate always caused partial alcoholysis of the potassium salt. In one particular experiment with 2 cc. of the ethylate in excess and a temperature of 5° complete alcoholysis took place; the amount of the monohydroxamic acid recovered as copper salt was almost quantitative. Rise in temperature favors alcoholysis. In all cases when alcoholysis took place, the odor of ethyl benzoate could be detected.

sym.-**Di-benzylmethylmethyl-urea,** $[(C_7H_7)(CH_3)CH.NH]_2CO$.—Two g. of the *dl*-benzoyl ester was converted into the potassium salt by the method described above.

The salt, collected quickly on a filter, was washed with cold dry ether, and dissolved in 40 cc. of water cooled to 5°. The salt dissolved quickly to give a clear solution. When the temperature of the solution reached 15–20° a turbidity developed. The solution was heated on the water-bath for one hour. This is necessary to hydrolyze the isocyanate completely since it is hydrolyzed very slowly at room temperature. The urea was collected and recrystallized.

sym.-Di-benzylmethylmethyl-urea crystallized from solution in hot ethyl acetate or acetone in needles melting at 199°. It was soluble in hot alcohol, and insoluble in water.

Anal. Subs., 0.1720: N, 14.9 cc. (26°, 760 mm.), over water. Calcd.: N, 9.46. Found: 9.56.

In an entirely similar manner the benzoyl esters of the dextro-acid, and of the mixed levo acid were converted into their potassium salts, and allowed to rearrange in water solution. Both esters gave a urea melting at 198–199°, and 0.30 g. of this urea dissolved in 25 cc. of alcohol showed no appreciable optical rotation.

d-Benzylmethyl-acetazide

$(C_7H_7)(CH_3)CH.CO.N_3$

This azide was prepared from *d*-benzylmethyl-acetyl chloride. *d*-

Benzylmethyl-acetyl chloride can be prepared by the action of phosphorus pentachloride on *d*-benzylmethylacetic acid, or by the action of thionyl chloride on this acid.[18] The chloride used in these experiments was prepared according to the method of Pickard and Yates.[19] The tendency of the chloride to racemize is probably less when thionyl chloride is used. Racemization of the chloride during distillation occurred in one experiment only. The chloride boiled at 105° (9 mm.), and gave a rotation of +12.70° in a 50mm. tube at 20° without solvent, as compared with +25.5° obtained by Kipping and Hunter, and +26.2° obtained by Pickard and Yates, in a 100mm. tube.

Preparation of *d*-Benzylmethyl-acetazide.—By the action of sodium azide on this chloride, *d*-benzylmethyl-acetazide was prepared. Ten g. of the acid chloride was dissolved in dry ether and cooled to 0°. To this solution was added 10 g. of powdered sodium azide recrystallized from water by precipitation with acetone. The suspension was stirred mechanically for 12 hours, while the temperature was kept near 5°. An azotometer was joined to the reaction flask to detect any decomposition of the azide. No gas evolution took place at this temperature. However, when the temperature was raised to that of the room, partial decomposition always occurred. The ether suspension was filtered, and the filtrate evaporated in a vacuum. The temperature throughout the whole preparation was not allowed to exceed 5°. Roughly, 10 g. of the azide was obtained. In a wholly similar manner the *dl*-azide was prepared.

d-Benzylmethyl-acetazide was an unstable, colorless liquid which decomposed slowly at about 10°. It was soluble in the common organic solvents. In water the isocyanate first formed was hydrolyzed to give *sym.*-di-benzylmethylmethyl-urea; m. p., 198–199°.

d-Benzylmethyl-acetazide, without solvent, in a 50mm. tube at 5° gave a rotation of +30.77°.

Rearrangement of *d*-Benzylmethyl-acetazide.—Eight g. of *d*-benzylmethyl-acetazide was dissolved in benzene, and rearrangement allowed to take place at 35°. After evolution of nitrogen had ceased completely, the solution was distilled under diminished pressure. The *d*-isocyanate boiled at 82° (5 mm.). A very small residue, probably a polymer, remained in the distilling flask. The *d*-isocyanate without solvent gave a rotation of +28.75° at 20° in a 50mm. tube; 0.9433 g. dissolved in benzene and diluted to 50 cc. gave a rotation in a 200mm. tube of +1.98°; $[\alpha]_D^{20°} = +52.5°$. The *dl*-isocyanate, prepared in a similar manner, boiled at 78° (3 mm.).

The rearrangement of the azide to the isocyanate was studied quantitatively. A solution of 1.095 g. of the *dl*-azide in 40 cc. of benzene was allowed to rearrange, and the volume of the nitrogen collected over benzene in an azotometer. N. 174.0 cc. (28°, 740 mm.). N (corr., v. p. of benzene at 28°, 117 mm.), 125.2 cc. Calcd. 129.7 cc. Completeness of the rearrangement, 97%.

The purity of the isocyanate was established by three methods.

a. Determination of its molecular weight by the freezing-point method.

Mol. Wt. Subs., 0.7652: 17.4020 g. of benzene; Δt, 1.385°. Calcd.: 161.0°. Found: 158.7.

b. Quantitative conversion to the *sym.*-di-benzylmethylmethyl-urea. When 1.2574 g. of the isocyanate was added to water and the mixture heated on the water-

[18] Ref. 14 c, p. 1008.

[19] Pickard and Yates, *Trans. Chem. Soc.*, **95**, 1019 (1909).

bath for one hour, the odor of the isocyanate was completely lost. The urea was collected on a filter and dried; yield, 2.2619 g.; calculated yield, 2.3117 g.; completeness of the reaction, practically 98%.

c. By analysis.

Anal. *d*-Isocyanate. Subs., 0.414 (1): N, 31.2 cc. (21°, 748 mm.), over water. Calcd.: N, 8.70. Found: 8.40.

dl-Isocyanate. Subs., 0.288 (2): N, 21.5 cc. (20°, 762 mm.), over water. Found: 8.51.

sym.-**Di-benzylmethylmethyl-urea,** $[(C_7H_7)(CH_3)CH.NH]_2CO$.—A mixture of 1.50 g. of the *d*-isocyanate and water was placed on a water-bath. At the end of one hour the odor of isocyanate was completely lost. The urea was collected on a filter and 0.60 g. dissolved in 50 cc. of methyl alcohol gave no appreciable rotation at 20°. This is nearly a saturated solution, and for that reason no solution of greater concentration was used. Two recrystallizations from acetone gave a white crystalline compound melting at 198°. The urea prepared from the *dl*-isocyanate in a wholly similar manner melted at 198–199°. These melting points seem to be identical with those of the urea prepared from the hydroxamic acid.

d-**Benzylmethylmethyl-urea,** $(C_7H_7)(CH_3)CH.NHCO.NH_2$.—Two g. of *d*-benzylmethylmethyl-isocyanate was dissolved in benzene, and dry ammonia gas passed through the solution. In a few minutes a precipitate of the urea was obtained. This was collected on a filter; 1.9 g. of dry product was obtained. Recrystallization from alcohol and water gave a solid melting at 136°.

A solution of 1.870 g. in acetone, total volume 50 cc., gave a rotation of +0.80° in a 200mm. tube at 20°; $[\alpha]_D^{20°} = +10.7°$.

The *dl*-urea was prepared in a similar manner. Two recrystallizations from alcohol and water gave a solid melting at 149°. A mixture of 5% of the *dl*-urea and 95% of the *d*-urea gave a fused mass that began to melt at 133°.

d-Benzylmethylmethyl-urea is a colorless crystalline compound soluble in acetone, in alcohol, in ethyl acetate, in chloroform, in hot water and in hot benzene. It is somewhat soluble in cold water, in ether and in benzene, and insoluble in ligroin.

Anal. Subs., 0.2401: N, 34.4 cc. (25°, 760 mm.), over water. Calcd.: N, 15.7. Found: 15.9.

d-**Benzylmethyl-methylamine Hydrochloride,** $(C_7H_7)(CH_3)CH.NH_3Cl$.—When 1.296 g. of *d*-benzylmethylmethyl-isocyanate was placed in a small flask, together with 4 cc. of concd. hydrochloric acid a reaction started immediately, but progressed slowly. The flask was kept cool by allowing water to play over it. After an hour the two layers had disappeared, and carbon dioxide ceased to be evolved. Near the end of the reaction the flask was warmed to 38°. The solution was diluted with water and extracted thrice with ether to remove any unchanged isocyanate. The ether extract gave no residue of isocyanate upon evaporation. The solution gave a rotation of +1.88° in a 200mm. tube at 20°.

The water solution was evaporated to dryness. A white, crystalline, hygroscopic salt was left. This was washed with ether and dried in the oven at 80°. The amount of chloride obtained was 1.25 g., melting at 147°. 1.20 g. dissolved in 25 cc. of water gave a rotation of +1.60° in a 200mm. tube at 20°, $[\alpha]_D^{20°} = +16.6°$.

Anal. Subs., 0.5150: AgCl, 0.4286. Calcd.: Cl, 20.7. Found: 20.6.

Decomposition of the Azide. Determination of the Reaction Velocity.—A solution of 0.5161 g. of *dl*-benzylmethyl-acetazide in 40 cc. of benzene was immersed in a constant-temperature bath regulated for 35° and kept constant to 0.1°. To the flask was

[20] See Ref. 12 for equation.

joined an azotometer and the nitrogen evolved was collected over benzene. A table giving the results follows.

TABLE I

REACTION VELOCITY OF RACEMIC BENZYLMETHYL-ACETAZIDE[20]

Time, min.	15	45	60	75	90	120	150	165	180	
Corr. vol. N, cc.	9.60	25.07	30.47	35.24	39.42	45.57	49.60	51.30	53.06	60.07
$k_{35}° \times 10^3$	11.60	11.98	11.78	11.77	11.85	11.83	11.63	11.67	11.91	Av. 11.78

Summary

The preparation and properties of several new compounds have been discussed. Benzylmethyl-acethydroxamic acid, and benzylmethyl-acetazide were prepared in their dextro, racemic and mixed levo modifications, and several of their derivatives were studied.

Evidence is submitted in this paper to show that certain optically active derivatives of optically active acids, when they rearrange, give optically active rearrangement products. The rearrangement of *d*-benzylmethyl-acethydroxamic acid and of *d*-benzylmethyl-acetazide was studied. Optically active rearrangement products were not obtained in the experiments with benzylmethyl-acethydroxamic acid; but rearrangement of *d*-benzylmethyl-acetazide was found to give an optically active isocyanate which could be converted into an optically active amine hydrochloride, and into an optically active monosubstituted urea. An explanation of this reaction is suggested.

The velocity of rearrangement of benzylmethyl-acetazide was measured at 35°, and was found to correspond to that of a unimolecular reaction; the value of the constant was $k_{35°} = 0.01178$.